AMENDMENTS TO THE SPECIFICATION

Please replace the paragraph beginning on line 13 of page 27 of the substitute specification filed September 13, 2002 with the following amended paragraph:

--One methodology that can be used to obtain human antibodies that are specifically reactive with human antigens is the production of a transgenic mouse harboring the human immunoglobulin transgene constructs of this invention. Briefly, transgenes containing all or portions of the human immunoglobulin heavy and light chain loci, or transgenes containing synthetic "miniloci" (described *infra*, and in ~~copending applications~~ U.S.S.N. 08/352,322, filed 7 December 1994 (issued as U.S. Patent No. 5,625,126 on April 29, 1997), U.S.S.N. 07/990,860, filed 16 December 1992 (issued as U.S. Patent No. 5,545,806 on August 13, 1996), U.S.S.N. 07/810,279 filed 17 December 1991 (issued as U.S. Patent No. 5,569,825 on October 29, 1996), U.S.S.N. 07/904,068 filed June 23, 1992 (now abandoned); U.S.S.N. 07/853,408, filed 18 March 1992 (issued as U.S. Patent No. 5,789,650 August 4, 1998), U.S.S.N. 07/574,748 filed August 29, 1990 (now abandoned), U.S.S.N. 07/575,962 filed August 31, 1990 (now abandoned), and PCT/US91/06185 filed August 28, 1991, each incorporated herein by reference) which comprise essential functional elements of the human heavy and light chain loci, are employed to produce a transgenic nonhuman animal. Such a transgenic nonhuman animal will have the capacity to produce immunoglobulin chains that are encoded by human immunoglobulin genes, and additionally will be capable of making an immune response against human antigens. Thus, such transgenic animals can serve as a source of immune sera reactive with specified human antigens, and B-cells from such transgenic animals can be fused with myeloma cells to produce hybridomas that secrete monoclonal antibodies that are encoded by human immunoglobulin genes and which are specifically reactive with human antigens.--

Please replace the paragraph beginning on line 19 of page 54 of the substitute specification filed September 13, 2002 with the following amended paragraph:

--A genomic fragment containing all of the necessary gene segments and regulatory sequences from a human light chain locus may be similarly constructed. Such transgenes are constructed as described in the Examples and in copending application, entitled "Transgenic Non-Human Animals Capable of Producing Heterologous Antibodies," filed August 29, 1990, under U.S.S.N. 07/574,748 (now abandoned).--

Please replace the paragraph beginning on line 19 of page 55 of the substitute specification filed September 13, 2002 with the following amended paragraph:

-- In the preferred embodiments utilizing *in vivo* transgene construction, each overlapping DNA fragment preferably has an overlapping substantially homologous DNA sequence between the end portion of one DNA fragment and the end portion of a second DNA fragment. Such overlapping portions of the DNA fragments preferably comprise about 500 bp to about 2000 bp, most preferably 1.0 kb to 2.0 kb. Homologous recombination of overlapping DNA fragments to form transgenes *in vivo* is further described in commonly assigned U.S. Patent Application entitled "Intracellular Generation of DNA by Homologous Recombination of DNA Fragments" filed August 29, 1990, under U.S.S.N. 07/574,747 (now abandoned). --

Please replace the paragraph beginning on line 3 of page 59 of the substitute specification filed September 13, 2002 with the following amended paragraph:

-- At least one, and preferably more than one, V gene segment is used to construct the heavy chain minilocus transgene. Rearranged or unrearranged V segments with or without flanking sequences can be isolated as described in copending applications, U.S.S.N. 07/574,748 filed August 29, 1990 (now abandoned), PCT/US91/06185 filed August 28, 1991, and U.S.S.N.

07/810,279 filed December 17, 1991 (issued as U.S. Patent No. 5,569,825 on October 29, 1996), each of which is incorporated herein by reference.

Please replace the paragraph beginning on line 11 of page 59 of the substitute specification filed September 13, 2002 with the following amended paragraph:

-- Rearranged or unrearranged V segments, D segments, J segments, and C genes, with or without flanking sequences, can be isolated as described in copending applications U.S.S.N. 07/574,748 filed August 29, 1990 (now abandoned) and PCT/US91/06185 filed August 28, 1991. --

Please replace the paragraph beginning on line 18 of page 59 of the substitute specification filed September 13, 2002 with the following amended paragraph:

-- Thus, for example, an immunoglobulin heavy chain minilocus transgene construct, e.g., of about 75 kb, encoding V, D, J and constant region sequences can be formed from a plurality of DNA fragments, with each sequence being substantially homologous to human gene sequences. Preferably, the sequences are operably linked to transcription regulatory sequences and are capable of undergoing rearrangement. With two or more appropriately placed constant region sequences (e.g., μ and γ) and switch regions, switch recombination also occurs. An exemplary light chain transgene construct can be formed similarly from a plurality of DNA fragments, substantially homologous to human DNA and capable of undergoing rearrangement, as described in copending application, U.S.S.N. 07/574,748 filed August 29, 1990 (now abandoned). --

Please replace the paragraph beginning on line 23 of page 66 of the substitute specification filed September 13, 2002 with the following amended paragraph:

--"Antisense polynucleotides" are polynucleotides that: (1) are complementary to all or part of a reference sequence, such as a sequence of an endogenous Ig C_H or C_L region, and (2)

which specifically hybridize to a complementary target sequence, such as a chromosomal gene locus or a Ig mRNA. Such complementary antisense polynucleotides may include nucleotide substitutions, additions, deletions, or transpositions, so long as specific hybridization to the relevant target sequence is retained as a functional property of the polynucleotide. Complementary antisense polynucleotides include soluble antisense RNA or DNA oligonucleotides which can hybridize specifically to individual mRNA species and prevent transcription and/or RNA processing of the mRNA species and/or translation of the encoded polypeptide (Ching et al., Proc. Natl. Acad. Sci. U.S.A. 86:10006-10010 (1989); Broder et al., Ann. Int. Med. 113:604-618 (1990); Loreau et al., FEBS Letters 274:53-56 - (1990); Holcenberg et al., W091/11535; U.S.S.N. 07/530,165 ("New human CRIPTO gene"; issued as U.S. Patent No. 5,256,643 on October 26, 1993); W091/09865; W091/04753; W090/13641; and EP 386563, each of which is incorporated herein by reference). An antisense sequence is a polynucleotide sequence that is complementary to at least one immunoglobulin gene sequence of at least about 15 contiguous nucleotides in length, typically at least 20 to 30 nucleotides in length, and preferably more than about 30 nucleotides in length. However, in some embodiments, antisense sequences may have substitutions, additions, or deletions as compared to the complementary immunoglobulin gene sequence, so long as specific hybridization is retained as a property of the antisense polynucleotide. Generally, an antisense sequence is complementary to an endogenous immunoglobulin gene sequence that encodes, or has the potential to encode after DNA rearrangement, an immunoglobulin chain. In some cases, sense sequences corresponding to an immunoglobulin gene sequence may function to suppress expression, particularly by interfering with transcription. --

Please replace the paragraph beginning on line 9 of page 278 of the substitute specification filed September 13, 2002 with the following amended paragraph:

-- All publications and patent applications herein are incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference. Commonly assigned applications U.S.S.N. 08/544,404

filed 10 October 1995 (issued as U.S. Patent No. 5,770,429 on June 23, 1998), U.S.S.N. 08/352,322, filed 7 December 1994 (issued as U.S. Patent No. 5,625,126 on April 29, 1997), U.S.S.N. 08/209,741 filed 9 March 1994 (now abandoned), U.S.S.N. 08/165,699 filed 10 December 1993 (now abandoned) and U.S.S.N. 08/161,739 filed 03 December 1993 (now abandoned), which is a continuation-in-part of 08/155,301 filed 18 November 1993 (now abandoned), W092/03918, USSN 07/810,279 filed 17 December 1991 (issued as U.S. Patent No. 5,569,825 on October 29, 1996), USSN 07/853,408 filed 18 March 1992 (issued as U.S. Patent No. 5,789,650 August 4, 1998), USSN 07/904,068 filed 23 June 1992 (now abandoned), USSN 07/990,860 filed 16 December 1992 (issued as U.S. Patent No. 5,545,806 on August 13, 1996), W093/12227, and USSN 08/053,131 filed 26 April 1993 (issued as U.S. Patent No. 5,661,016 on August 26, 1997) are each incorporated herein by reference. --